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FETTEROLF, BRANDON J	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/734,589	GOVINDAN, SERENGULAM V.	
	Examiner	Art Unit	
	BRANDON J. FETTEROLF	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-8,13-15,17-34,36-45 and 48-73* is/are pending in the application.

4a) Of the above claim(s) *5-8,51-62 and 68-73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 13-15, 17-34, 36-45, 48-50 and 63-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

The Election filed on 1/14/2008 in response to the Restriction Requirement of **December** 14, 2008 has been entered. Applicant's election of antibodies comprising a light chain variable region sequence comprising the CDR sequences KASQDVSIAVA (SEQ ID NO: 7), SASYRYT (SEQ ID NO: 8) and QQHYITPLT (SEQ ID NO: 9) and heavy chain variable region sequence comprising the CDR sequences NYGMN (SEQ ID NO: 10), WINTYTGEPTYTDDFKG (SEQ ID NO: 11) and GGFGSSYWYFDV (SEQ ID NO: 12) found on the RS7 antibody.

Claims 1, 5-8, 13-15, 17-34, 36-45, 48-73 are pending.

Claims 5-8 and 51-62 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 68-73 are withdrawn from consideration as being drawn to non-elected species.

Claims 1, 13-15, 17-34, 36-45, 48-50 and 63-67 are currently under consideration.

Rejections Withdrawn:

The rejection of Claims 25-26, 44 and 63-66 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description is withdrawn in view of Applicants remarks starting on page 20.

The rejection of claims 1, 13-15, 17, 19, 21-24, 27-31, 33-34, 36, 38, 40-43 and 48-50 under 35 U.S.C. 103(a) as being unpatentable over Chari et al. (WO 01/24763 A2, 2001) in view of Zhao et al. (US 6,716,821, 2004) is withdrawn in view of Applicants amendments to incorporate the limitations of said thiol-reactive group is a maleimido or vinylsulfone which links to thiol groups of said antibody.

New Rejections Upon further consideration:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 15, 17, 18-30, 32-34, 36-45, 48-50 and 63-67 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical characteristics and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (Federal register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3) and (see MPEP 2164).

The claims encompass an immunoconjugate comprising an antibody, a chemotherapeutic agent and a linker comprising (i) a thiol-reactive functional group that binds to a thiol group on the antibody and (ii) a genus of water solubilizing moiety useful for the treatment of cancer. Therefore, the claims encompass a genus of molecules defined solely by its principal biological property, e.g., water solubilizing moiety, which is simply a wish to know the identity of any material with that biological property. Accordingly, there is insufficient written description encompassing a "water-solubilizing moiety" because the relevant identifying characteristics of the genus such as structure or other physical and/or chemical characteristics of a "water solubilizing moiety" are not set forth in the specification as-filed, commensurate in scope with the claimed invention. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.

The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (see page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (see Vas-Cath at page 1116).

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddles v.Baird, 30 USPQ2d 1481, 1483. In Fiddles v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Thus, the specification fails to describe these DNA sequences. The Court further elaborated that generic statements are not adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Per the *Enzo* court's example, (*Enzo Biochem, Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (CA FC 2002) at 1616) of a description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) couched "in terms of its function of lessening inflammation of tissues" which, the court stated, "fails to distinguish any steroid from others having the same activity or function" and the expression "an antibiotic penicillin" fails to distinguish a particular penicillin molecule from others possessing the same activity and which therefore, fails to satisfy the written description requirement. Similarly, a water solubilizing moiety does not distinguish any a particular water solubilizing moieties from others having the same activity or function and as such does not satisfy the written-description requirement. Applicant has not disclosed any relevant, identifying characteristics, such as structure or other physical and/or chemical properties, sufficient to show possession of the claimed genus. Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required. A description of what a material does, rather than what it is, usually does not suffice. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

In the absence of structural characteristics that are shared by members of the genus of a water solubilizing moieties; one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 13-14, 17-24, 27-31, 33-34, 36-43 and 48-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chari et al. (WO 01/24763 A2, 2001, of record) in view of Hsel et al. (US 7,122,636, filed 2000).

Chari et al teach (page 2, lines 11-14 and page 5, lines 30-31) an immunoconjugate comprising a cell binding agent and at least one therapeutic agent for killing a selected cell population, wherein the cell binding agent is a monoclonal antibody or fragment thereof (i.e. Fv, Fab, Fab' and $F(ab')_2$) and the therapeutic agent is an anti-mitotic agent that is linked to the antibody via a linking group. With regards to the antibody, the WO publication teaches (page 17, lines 3-5) that the choice of the appropriate antibody depends on the cell population that is to be targeted. For example, Chari et al. teach (page 17, lines 6-13) that the monoclonal antibody anti-B4, which binds to the CD19 antigen on B cells, can be used to target B cells. Alternatively, the WO publication teaches (page 17, lines 23-31) that antibody or fragment thereof that is specific for lung cancer such as an antibody that binds to an epitope on the CD56 antigen expressed on small cell lung cancers. With regards to the linking group, Chari et al. teach (page 6, lines 1-2) that suitable linking groups include, but are not limited to, esterase labile groups. Moreover, the WO publication teaches (page 6, lines 4-14, page 7, lines 1-5, page 9, formula II and/or III and page 21, lines 28-30) that the linking group is part of a chemical moiety having a peptide such as N-methyl-cysteine or N-methyl-alanine, covalently bound at the C-terminus to an anti-mitotic agent, such as a maytansinoid derivative, via an ester linkage, e.g., alpha carboxylic acid, and at the N-terminus to the cell-binding agent via a disulfide bond. As a result, the WO publication teaches (page 22, lines 1-2) the conjugates would have 1 to 10 drug molecules per antibody molecule. Moreover, Chari et al. teach (page 30, lines 9-22) that the immunoconjugates may be administered in a suitable form via i.v.. Thus, while Chari et al. do not characterize an antibody specific for an antigen expressed on small

cell lung cancer as an antibody specific for an antigen expressed on a carcinoma cell, the claimed functional limitation would be an inherent property because as evidenced by Dictionary.com (see attached), small cell lung cancer is also referred to as small-cell lung carcinoma. Moreover, although Chari et al. does not specifically recite that the immunoconjugate is formulated for parental administration, the claimed functional limitation would be an inherent property because as evidenced by Stedman's Medical Dictionary (see attached), the term parental refers to the introduction of substances to an organism by intravenous, subcutaneous, intramuscular, or intramedullary injection. Thus, the claimed immunoconjugate appears to be the same as the prior art. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Chari et al. do not explicitly teach that the linker further comprises a water-solubilizing moiety between the therapeutic moiety and the cell binding agent, wherein the water-solubilizing agent is an aminopolycarboxylate such as PEG.

Hsel et al. teach a conjugated formed by one or more antibody fragments covalently attached to one or more nonproteinaceous polymer molecules (column 7, lines 29-21). In particular, the patent teaches that the antibodies include, but are not limited to, antibodies comprising an antigen binding site that binds to a polypeptide selected from the group consisting of vascular endothelial growth factor (VEGF), human p185 receptor-like tyrosine kinase (HER2), human CD20, human CD18, human CD11a, human IgE, human apoptosis receptor (Apo-2), human tumor necrosis factor-a (TNF-a), human tissue factor, human a4b7 integrin, human GPIIb-IIIa integrin, human epidermal growth factor receptor (EGFR), human CD3, and human iterleukin-2 receptor a-chain (TAC) (column 7, lines 45-59). Moreover, the patent teaches that the antibodies include bispecific and heteroconjugate antibody fragments having specificities for at least two different antigens (column 64, lines 27-46). With regards to the nonproteinaceous polymer molecules, the patent teaches that nonproteinaceous polymer molecules include, but are not limited to, PEG (column 65, lines 24-60). The patent further teaches that the antibody conjugates can be produced by reacting

the free sulfhydryl group of the antibody with a maleimido substituted PEG (column 66, lines 22-48). In addition, the patent teaches that the conjugates can be modified to incorporate one or more small molecule toxins. For example, the patent teaches that maytansine can be converted to May-ss-Me, which is reduced to MaySH3 and reacted with the modified fragment to generate a maytansinoid-derivatized antibody (column 69, lines 39-49). Lastly, the patent teaches that the conjugates exhibit substantially improved half-life, mean residence time, and/or clearance rate in circulation as compared to the underivatized parental antibody fragment (abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the reference so as to modify the conjugate as taught by Chari et al. include a PEG molecule in view of the teachings of Hsel et al.. One would have been motivated to do so because Hsel et al. clearly teaches conjugating maytansines to PEG-antibody conjugates. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the conjugate as taught by Chari et al. include a PEG molecule in view of the teachings of Hsel et al., one would achieve improved half-life, mean residence time, and/or clearance rate in circulation.

Claims 25 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chari et al. (WO 01/24763 A2, 2001) in view of Hsel et al. (US 7,122,636, filed 2000), as applied to claims 1, 13-14, 17-24, 27-31, 33-34, 36-43 and 48-50, in further view of Newton et al. (Blood 2001; 97: 528-535, of record).

Chari et al. in view of Hsel et al. teach an immunoconjugate comprising a cell binding agent and at least one therapeutic agent for killing a selected cell population, wherein the conjugate comprises a water soluble PEG linking group and the cell binding agent is a monoclonal antibody or fragment thereof (i.e. Fv, Fab, Fab' and $F(ab')_2$) and the therapeutic agent is an anti-mitotic agent that is linked to the antibody via a linking group. With regards to the antibody, the WO publication teaches (page 17, lines 3-5) that the choice of the appropriate antibody depends on the cell population that is to be targeted. For example, Chari et al. teach (page 17, lines 6-13) that the monoclonal antibody anti-B4 which is a murine IgG1, that binds to the CD19 antigen on B cells can be used to target B cells. Alternatively, the WO publication teaches (page 17, lines 23-31) that

antibody or fragment thereof that is specific for lung cancer such as an antibody that binds to an epitope on the CD56 antigen expressed on small cell lung cancers.

Chari et al in view of Hsel et al. do not explicitly teach that the targeting moiety is the antibody LL2.

Newton et al. teach (abstract) an immunoconjugate comprising LL2 covalently linked to the ribonuclease, onconase, wherein LL2 is an anti-CD22 monoclonal antibody against B-cell lymphoma.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the immunoconjugate as taught by Chari et al. in view of Hsel et al. with a monoclonal LL2 antibody in view of the teachings of Newton et al.. One would have been motivated to do so because as taught by Newton et al., the murine anti-CD22 monoclonal antibody (LL2) was developed for imaging and treatment of non-Hodgkin B-cell lymphomas (NHL). Thus, one of ordinary skill in the art would have a reasonable expectation of success that by incorporating LL2 into the immunoconjugate of Chari in view of the teachings of Newton, one would achieve an immunoconjugate which comprises a targeting agent specific for Non-Hodgkin B-cell lymphomas.

Claims 63-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chari et al. (WO 01/24763 A2, 2001, of record) in view of Hsel et al. (US 7,122,636, filed 2000), as applied to claims 1, 13-14, 17-24, 27-31, 33-34, 36-43 and 48-50, in further view of Govindan et al. (US 7,238,785, 3/1/2002).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior

inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Chari et al. in view of Hsel et al. teach an immunoconjugate comprising a cell binding agent and at least one therapeutic agent for killing a selected cell population, wherein the conjugate comprises a water soluble PEG linking group and the cell binding agent is a monoclonal antibody or fragment thereof (i.e. Fv, Fab, Fab' and $F(ab')_2$) and the therapeutic agent is an anti-mitotic agent that is linked to the antibody via a linking group. With regards to the antibody, the WO publication teaches (page 17, lines 3-5) that the choice of the appropriate antibody depends on the cell population that is to be targeted. For example, Chari et al. teach (page 17, lines 6-13) that the monoclonal antibody anti-B4 which is a murine IgG1, that binds to the CD19 antigen on B cells can be used to target B cells. Alternatively, the WO publication teaches (page 17, lines 23-31) that antibody or fragment thereof that is specific for lung cancer such as an antibody that binds to an epitope on the CD56 antigen expressed on small cell lung cancers.

Chari et al in view of Hsel et al. do not explicitly teach that the targeting moiety is the RS7.

Govindan et al. teach a monospecific monoclonal antibody and fragments thereof that recognize a tumor associated antigen defined as epithelial glycoprotien-1 (EGP-1) (column 2, lines 54-57). In particular, the patent refers to this antibody as humanized RS7 mAb which comprises CDR regions for the light and heavy chain which encompass the sequences claimed in claim 7 of the instant application (column 3, lines 6-39). Moreover, the patent teaches that the antibodies are useful for targeting tumor cells, wherein the antibodies are conjugated to a therapeutic agent, including but not limited to, chemotherapeutic agents selected from the group consisting of nitrogen mustard, ethylenimine derivative, alkyl sulfonate, nitrosourea, triazene, folic acid analog, anthracycline, taxane, COX-2 inhibitor, tyrosine kinase inhibitor, pyrimidine analog, purine analog, antibiotic, enzyme, epipodophyllotoxin, platinum coordination complex, vinca alkaloid, substituted urea, methyl hydrazine derivative, adrenocortical suppressant, antagonist, endostatin taxol, camptothecins, doxorubicin, doxorubicin analog, and a combination thereof (column 4, lines 38-60).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the immunoconjugate as taught by Chari et al. in view of Hsel et al. with a monoclonal RS7 antibody in view of the teachings of Govindan et al. One would have been motivated to do so because as taught by Govindan et al., RS7 antibodies were developed for treatment of tumors, and further, useful as cancer cell targeting therapeutic conjugates. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by incorporating RS7 into the immunoconjugate of Chari in view of the teachings of Govindan et al., one would achieve an immunoconjugate which comprises a targeting agent specific for tumors expressing the tumor antigen defined as epithelial glycoprotein-1.

Therefore, No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRANDON J. FETTEROLF whose telephone number is (571)272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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